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pH-Programmable Sequential Dissolution of Multilayer Stacks of Hydrogen-Bonded Polymers

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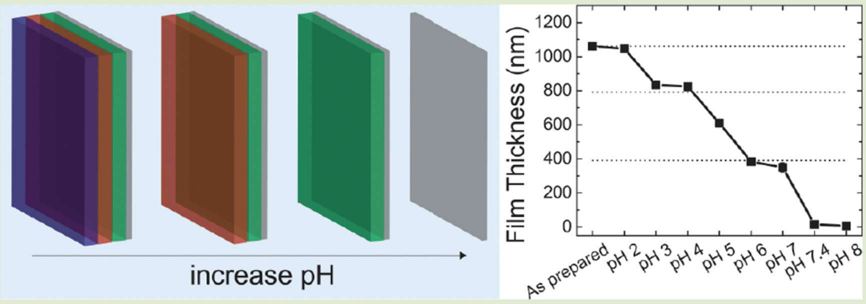
Supporting Information



ABSTRACT: We report that the interlayer diffusion of polymer chains within heterostructured hydrogen-bonded multilayer films depends on the stacking order: polymers diffuse more when high pH stability polymer pairs are assembled on top of low pH stability polymer pairs. By varying the stacking sequence, the fraction of the film that is released from the substrate can be tuned to achieve sequential pH-programmed release of the multilayer film. Also, we show that a multifunctional freestanding film with tunable film thickness can be generated by appropriate stacking and subsequent thermal cross-linking.

Layer-by-Layer (LbL) assembled multilayer films driven by hydrogen-bonding interactions have been utilized in many applications where incorporating uncharged polymers and obtaining stimuli-responsive properties are desired,[1−6] including controlled delivery systems,[7,8] cellular and bacterial adhesion,[9,10] biomimetic materials,[11] and microreactors.[12] For example, in the area of drug delivery, hydrogen-bonding LbL structures offer the unique advantages of (i) dissolution at a designated pH condition (pH_{crit}) and (ii) the option to assemble multiple stacks, each with different composition and properties, to generate heterostructured architecture suitable for "programmable" release of multiple functional elements within one system. However, the development of multicompartment LbL films with distinctive functional regions has been limited due to interlayer diffusion, which results in a blended internal structure.[13] Although much work has been done to resolve this issue in analogous electrostatically assembled LbL structures,[14,15] control of interlayer diffusion in purely hydrogen-bonded LbL films remains an unsolved problem.[4,16−18] Therefore, of particular interest are strategies to control the internal structure of these hydrogen-bonded layer systems assembled in multiple stacks to generate complex functional platforms.

In this work, we demonstrate a simple method to minimize interlayer diffusion of polymer chains within multistack hydrogen-bonded multilayer films by assembling the constituent polymers in a specific stacking order. When a low pH stability hydrogen-bonding pair is assembled on top of a high pH stability pair, interlayer diffusion is minimized, resulting in selective removal of the low pH stability section of the stack while preserving the high pH stability region. The net result is an ability to create a complex hydrogen-bonded heterostructured architecture that sequentially dissolves with an increase in local pH conditions. In addition to generating this pH-programmable platform, we show that a freestanding film with tunable film thickness can be generated through appropriate stacking and subsequent thermal cross-linking. Also, we functionalize the freestanding multilayer film with fluorescent dye and magnetic nanoparticles to demonstrate that functional materials can be incorporated into these nanoscale freestanding films.

As a basis for these studies, we selected poly(vinyl alcohol) (PVA), either fully hydrolyzed (PVA_F) or partially hydrolyzed (PVA_P), and the weak polyacids, poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA), as the hydrogen bonding pairs, which have been reported to successfully assemble at low pH conditions (pH 2.0) and exhibit conformal and reproducible growth behavior (30−50 nm/bilayer).[5,19,20] Polyacids incorporated in these hydrogen-bonded multilayer films become increasingly ionized at pH conditions above the assembly pH, a trend which continues until the critical pH (pH_{crit}), when the film disassembles primarily due to the enhanced swelling driven by the ionization of the polyacids.[18] By varying the polyacid and the degree of hydrolysis of PVA,

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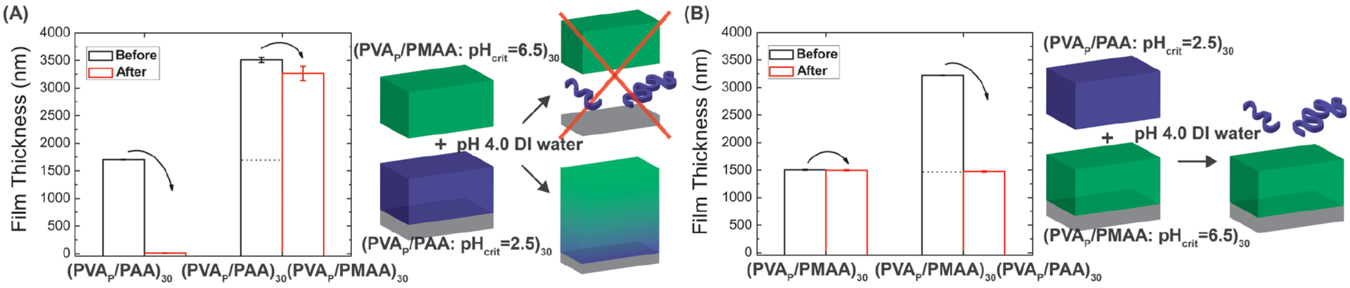


Figure 1. (A) Dry film thickness of (PVA$_P$/PAA: pH$_{crit}$ = 2.5)$_{30}$ and (PVA$_P$/PAA)$_{30}$(PVA$_P$/PMAA: pH$_{crit}$ = 6.5)$_{30}$ film on the substrate before and after exposure to pH 4.0 DI water for 2 h. (B) Dry film thicknesses of (PVA$_P$/PMAA)$_{30}$ and (PVA$_P$/PMAA)$_{30}$(PVA$_P$/PAA)$_{30}$ multilayers on the substrate before and after exposure to pH 4.0 DI water for 2 h. Schematic representation of film disassembly for two differently stacked multilayer films is shown on the right.

we observed distinctive pH$_{crit}$ values.[19] The pH stability of the complementary hydrogen-bonding pairs investigated in this paper decreased in the following order, (PVA$_P$/PMAA: pH$_{crit}$ = 6.5) > (PVA$_F$/PMAA: pH$_{crit}$ = 4.5) > (PVA$_P$/PAA: pH$_{crit}$ = 2.5). Here, the difference in the pH$_{crit}$ is attributed to the contribution of extra hydrophobic forces by acetate moieties in partially hydrolyzed PVA (PVA$_P$), similar to that reported previously.[11,12]

It has been well established that diffusion of an adsorbing polymer into a multilayer film can occur during the assembly, which can dramatically alter the physical properties of the film. To illustrate this effect with PVA-based multilayer film, differently stacked films consisting of (PVA$_P$/PAA: pH$_{crit}$ = 2.5) and (PVA$_P$/PMAA: pH$_{crit}$ = 6.5) were fabricated and subsequently exposed to pH 4.0 conditions as shown in Figure 1. The nomenclature for hydrogen-bonding based multilayer films follows conventions, (hydrogen bonding acceptor/donor)$_Z$, where Z is the total number of bilayers deposited.

In the first case (Figure 1A), where the 30 bilayers of high pH stability pair, (PVA$_P$/PMAA), were assembled on top of 30 bilayers of (PVA$_P$/PAA) film, exposure to pH 4.0 did not selectively dissolve the underlying layer of (PVA$_P$/PAA) and generate a freestanding film of (PVA$_P$/PMAA). Instead, only a slight decrease in overall film thickness was observed. A similar result has been reported previously,[18] where the high pH stability polymer pair (poly(N-vinylcaprolactam) (PVCL)/tannic acid (TA)) assembled on low pH stability polymer film enhanced the overall film pH stability. Additional related analysis on the PVA-based system is shown in the Supporting Information (Figure S1).

In the other case (Figure 1B), where 30 bilayers of (PVA$_P$/PAA: pH$_{crit}$ = 2.5) film were assembled on top of 30 bilayers of (PVA$_P$/PMAA: pH$_{crit}$ = 6.5) film, exposure to pH 4.0 DI water for 2 h completely removed the (PVA$_P$/PAA)$_{30}$, while the film retained on the glass substrate was similar in thickness to (PVA$_P$/PMAA)$_{30}$. This result suggests that when the low pH stability hydrogen-bonding pair is assembled on top of the high pH stability pair interlayer diffusion is minimized. A similar explanation for this asymmetric (in z-direction) diffusion has been reported based on an exchange of polymer chains in solution and those within the film during the assembly.[21,22]

Given that it is possible to assemble less pH-stable polymer pairs onto more pH-stable multilayer films without significant diffusion, more complex systems were explored in detail. Here, the stacking order and exposure pH of these individual systems were varied, while the number of bilayers was kept constant (10 bilayers for individual stacks). Four groups consisting of three different combinations of polymer pairs were studied: (PVA$_P$/PAA: pH$_{crit}$ = 2.5), (PVA$_F$/PMAA: pH$_{crit}$ = 4.5), and (PVA$_P$/PMAA: pH$_{crit}$ = 6.5).

All four groups were assembled at pH 2.0, and the dotted line in Figure 2 represents the dry film thicknesses measured between the assemblies of each 10 bilayers of a polymer pair. In contrast, the solid line represents the measured dry film thickness after incubation in designated pH conditions for 2 h. The first group (Figure 2A) was prepared on a glass substrate in a descending order of pH stability by assembling (PVA$_P$/PMAA: pH$_{crit}$ = 6.5)$_{10}$(PVA$_F$/PMAA: pH$_{crit}$ = 4.5)$_{10}$(PVA$_P$/PAA: pH$_{crit}$ = 2.5)$_{10}$; i.e., the (PVA$_P$/PAA) region is on the top. As shown in Figure 2A, stepwise dissolution behavior with increasing pH conditions was observed, revealing that interlayer diffusion is not significant and the critical pH behavior of the individual stacks is preserved despite the reported highly diffusive behavior of weakly associating hydrogen-bonding pairs.[4,16]

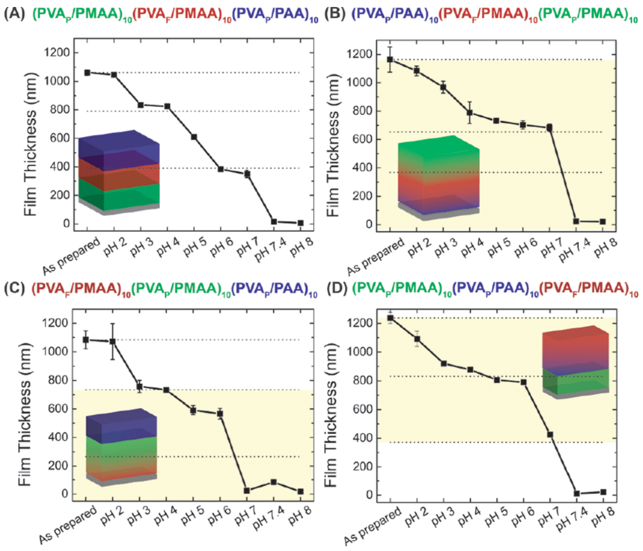


Figure 2. pH-triggered dissolution of (A) (PVA$_P$/PMAA: pH$_{crit}$ = 6.5)$_{10}$(PVA$_F$/PMAA: pH$_{crit}$ = 4.5)$_{10}$(PVA$_P$/PAA: pH$_{crit}$ = 2.5)$_{10}$, (B) (PVA$_P$/PAA)$_{10}$(PVA$_F$/PMAA)$_{10}$(PVA$_P$/PMAA)$_{10}$, (C) (PVA$_F$/PMAA)$_{10}$(PVA$_P$/PMAA)$_{10}$(PVA$_P$/PAA)$_{10}$, and (D) (PVA$_P$/PMAA)$_{10}$(PVA$_P$/PAA)$_{10}$(PVA$_F$/PMAA)$_{10}$. The shaded area represents the portion of the film where high pH stability polymer pairs were assembled on top of low pH stability polymer pairs.

The second group (Figure 2B) was prepared on a glass substrate in an ascending order of pH stability by assembling (PVA$_P$/PAA: pH$_{crit}$ = 2.5)$_{10}$(PVA$_F$/PMAA: pH$_{crit}$ =

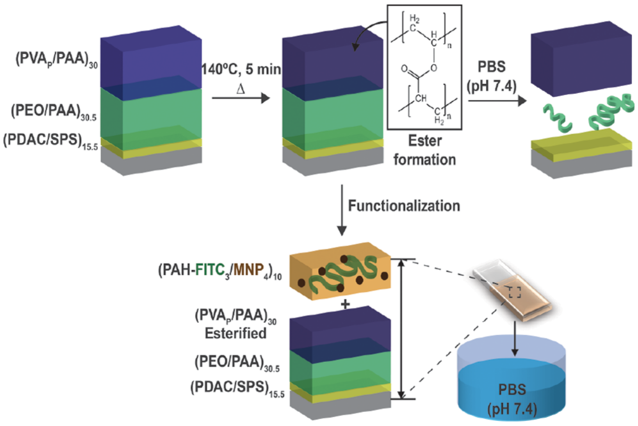
4.5)$_{10}$($\mathrm{PVA_P}$/PMAA: $\mathrm{pH_{crit}}$ = 6.5)$_{10}$. Compared to the previous case, the dissolution profile shows a monotonic decrease in film thickness with increase in pH up to pH 7.4, at which point the film completely dissolved. Similar behavior was observed previously[18] and was explained on the basis of partial removal of the weakly interacting polymer components from the film. Also, although the $\mathrm{pH_{crit}}$ of the bottommost stack (close to the substrate, ($\mathrm{PVA_P}$/PAA)$_{10}$) implies complete dissolution of the bottom stack above pH 3.0, this did not occur. Instead, complete dissolution took place at pH 7.4, which suggests that the individual stacks lost their independent stability characteristics as a result of interlayer diffusion of polymer chains during assembly. The same experiment in Figure 2A and Figure 2B was conducted at exposure pH of 4.0, 6.0, and 8.0 for longer times (up to 1 day) to reveal that a 2 h exposure is indeed sufficient to rule out the kinetic effects (data not shown). However, as discussed in more detail in the Supporting Information (Figure S2), it was observed that multiple wet-to-dry cycles in pH conditions just below $\mathrm{pH_{crit}}$ may facilitate dissolution of that film.

The third group (Figure 2C) was prepared with the two polymer pairs close to the substrate in increasing order of pH stability and the lowest pH stability polymer pair on top ($\mathrm{PVA_F}$/PMAA: $\mathrm{pH_{crit}}$ = 4.5)$_{10}$($\mathrm{PVA_P}$/PMAA: $\mathrm{pH_{crit}}$ = 6.5)$_{10}$($\mathrm{PVA_P}$/PAA: $\mathrm{pH_{crit}}$ = 2.5)$_{10}$. Upon exposure to pH 3.0, the top layer ($\mathrm{PVA_P}$/PAA) dissolved completely, while the underlying two polymer pairs with higher pH stability remained intact. With an increase in pH conditions, monotonic decrease in film thickness occurred similar to the second group (Figure 2B) until pH 7.0 where the local pH condition exceeds the $\mathrm{pH_{crit}}$ of the ($\mathrm{PVA_P}$/PMAA) pair and complete film dissolution was observed.

The last group (Figure 2D) was prepared on a glass substrate by assembling ($\mathrm{PVA_P}$/PMAA: $\mathrm{pH_{crit}}$ = 6.5)$_{10}$($\mathrm{PVA_P}$/PAA: $\mathrm{pH_{crit}}$ = 2.5)$_{10}$($\mathrm{PVA_F}$/PMAA: $\mathrm{pH_{crit}}$ = 4.5)$_{10}$. In this case, unusual dissolution behavior was observed. At pH 6.0, a 790 ± 16 nm thick film remained on the glass substrate even though both the polymer pairs assembled close to the surface, ($\mathrm{PVA_P}$/PAA) and ($\mathrm{PVA_F}$/PMAA), have $\mathrm{pH_{crit}} < 6.0$. Furthermore, in the case of exposure to pH 7.0, the residual film remaining on the glass substrate was 425 ± 4 nm thick, which is close to the as-prepared ($\mathrm{PVA_P}$/PMAA)$_{10}$ thickness of 372 ± 4 nm, and nondissolving freestanding films were generated. One possible explanation for this observation is interlayer diffusion or intermixing between layers, resulting in a new combination of polymer pairs. This four-component ($\mathrm{PVA_P}$, $\mathrm{PVA_F}$, PAA, PMAA) intermixing could result in the combination of $\mathrm{PVA_P}$/PMAA, which may explain the nondissolving freestanding film at pH 7.0.

The ability to generate multicompartment hydrogen-bonded structures can be further extended to fabricate multifunctional freestanding films containing PVA with controllable film thicknesses. Previously, we have demonstrated that the $\mathrm{PVA_P}$/PAA polymer pair has low pH stability ($\mathrm{pH_{crit}}$ = 2.5), but the presence of alcohol groups in PVA allows the formation of cross-links with carboxylic acid groups in PAA via thermally induced esterification, which enhances the pH stability to physiological pH conditions.[19] Thus, it was anticipated that a PVA-containing freestanding film could be generated by assembling a hydrogen-bonding polymer pair prior to the deposition of ($\mathrm{PVA_P}$/PAA) layers with the following characteristics: (i) higher pH stability than the ($\mathrm{PVA_P}$/PAA) pair to minimize interlayer diffusion and (ii) the inability to cross-link during thermal cross-linking to allow dissolution as a sacrificial layer. Here, poly(ethylene oxide) (PEO)/PAA was chosen because its dissolution pH has been reported to be 3.5,[23] which is higher than $\mathrm{PVA_P}$/PAA ($\mathrm{pH_{crit}}$ = 2.5); it also has been reported that the PEO/PAA system does not cross-link severely upon mild thermal treatment.[24] As shown in Scheme 1, 15.5 bilayers of (poly(diallyldimethylammonium chloride (PDAC)/poly(sodium 4-styrene-sulfonate) (SPS)) were first assembled on a glass substrate to improve subsequent assembly of (PEO/PAA)$_{30.5}$. The number of 15.5 bilayers was chosen arbitrarily; fewer bilayers (e.g., 5.5) work just as well. Then, 30 bilayers of ($\mathrm{PVA_P}$/PAA) multilayers were assembled on top of the (PEO/PAA) layers and thermally cross-linked at 140 °C for 5 min. Subsequent immersion in PBS buffer produced a freestanding film of cross-linked ($\mathrm{PVA_P}$/PAA)$_{30}$ with thickness of ~700 nm (Supporting Information, Figure S3). A control experiment was performed on a thermally treated system containing solely (PEO/PAA)$_{30.5}$ to confirm that the underlying layer completely dissolves after the selected heating protocol (Figure 3A).

Scheme 1. Fabrication of a $\mathrm{PVA_P}$/PAA Freestanding Film and Its Functionalized Form



Fabrication of nanoscale multifunctional freestanding films has been of significant interest in the field of layer-by-layer

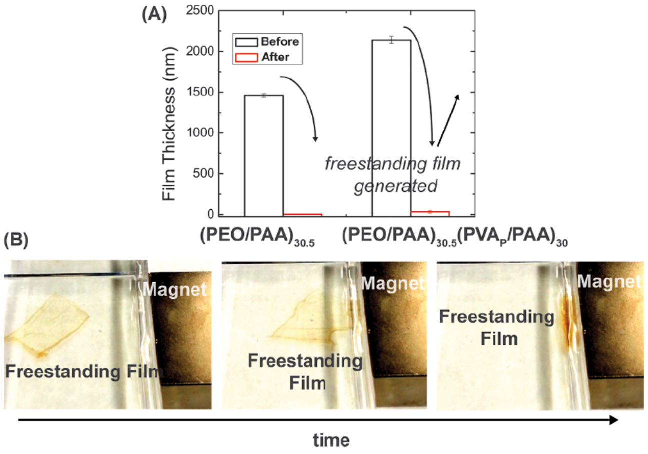


Figure 3. (A) Multilayer film retained on the glass substrate before and after exposure to PBS buffer solution (pH 7.4) for 2 h. (B) Fe_3O_4 superparamagnetic nanoparticles embedded in the freestanding multilayer film drives the film to a magnet by the external magnetic force.

assembly.[25] Although hydrogen-bonded freestanding films have been generated through other methods,[6,18,24,26] precise control over film thickness is often limited. On the other hand, our experimental technique allows not only facile pH-triggered release from the substrate but also robust additional functionalization capabilities to achieve PVA-based multifunctional freestanding films. A fluorescent-labeled freestanding film with potential in magnetic applications[13] was prepared by subsequently assembling functional materials on top of the $(PDAC/SPS)_{10.5}(PEO/PAA)_{30.5}(PVA_P/PAA)_{30}$ multilayer film cross-linked at 140 °C for 5 min. Anionic Fe_3O_4 superparamagnetic nanoparticles (MNPs) were alternately deposited with fluorescein-labeled poly(allylamine hydrochloride) (PAH-FITC) on top of this system and exposed to PBS buffer (pH 7.4) as shown in Scheme 1. As long as the subsequent functional LbL layers were assembled at pH conditions where thermally treated PEO/PAA is stable (below pH = 4.0), successful generation of a functionalized freestanding film was achieved. The freestanding multilayer film mounted on a glass substrate after exposure for 2 h in PBS buffer as well as the control samples are shown in the Supporting Information (Figure S4). Fe_3O_4 superparamagnetic nanoparticles embedded in the freestanding multilayer film can drive the film to a magnet through external magnetic forces as shown in Figure 3B. This freestanding film was stable in PBS buffer for over a month.

In summary, we show that when a low pH stability hydrogen-bonding pair is assembled on top of a high pH stability pair interlayer diffusion can be minimized, whereas it is significant in the opposite case. In addition, the fabrication of fluorescently labeled freestanding films with magnetically responsive properties revealed that understanding the nuances of interlayer diffusion in the hydrogen-bonded system can assist in the design of multifunctional freestanding ultrathin heterostructured films.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Contains pH-triggered dissolution study with blocking layers, pH-triggered dissolution study of $(PVA_P/PMAA)_{10}(PVA_F/PMAA)_{10}(PVA_P/PAA)_{10}$ with multiple wet-to-dry cycles, and fluorescence microscopy image of control experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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